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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Nozer M. Mehta, *et al.* | Confirmation No.: 2921

Serial No.: 10/761,481 | Group Art Unit: 1654

Filed: January 10, 2004 | Examiner: Jeffrey E. Russel

For: IMPROVED ORAL DELIVERY OF PEPTIDES

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF INVENTOR
WILLIAM STERN UNDER 37 C.F.R. §1.132

I, William Stern, hereby declare that:

1. I am a co-inventor named in the above-identified patent application, and I am familiar with the contents of the application.
2. Since 1991, I have been a Senior Research Scientist in the Protein Biochemistry Department at Unigene Laboratories, Inc. located in Fairfield, New Jersey, which is the Assignee of this application. I have several years of experience in the field of oral delivery of peptides and proteins and I am a named co-inventor of two United States patents, i.e., No. 5,912,014 issued June 15, 1999 and No. 6,086,918 issued July 11, 2000, directed to the oral delivery of such molecules. Prior to taking up my present position, I was employed as a Senior Scientist in the Protein Biochemistry Department at Unigene Laboratories from 1986 to 1990.
3. I received a Ph.D. degree In Biological Chemistry from the University of Michigan in 1972.
4. I have read and am familiar with (1) the Office Action mailed on November 26, 2007 by the Examiner in charge of the above-identified patent application and (2) the prior art references cited therein. I make this declaration in support of the patentability of the claimed invention.
5. I understand that this application contains claims to oral pharmaceutical compositions providing enhanced bioavailability of an orally delivered

physiologically active peptide (see, e.g., independent claim 1), as well as to a method for enhancing the bioavailability of an orally delivered physiologically active peptide agent (see, e.g., independent claim 45) and that the claims to both the composition and the method require a peptide agent amidated at a location that is not naturally amidated, i.e., to facilitate oral delivery and bioavailability of the peptide.

6. I am familiar with the relevant literature in this field that demonstrates that peptides, such as hormones and growth factors, often contain a C-terminal amide group which is essential for, or which enhances, the biological activity of the subject peptide. I am also familiar with the literature that demonstrates that it is possible to amidate a peptide that is not naturally amidated by chemical or enzymatic means.

7. However, despite my years of experience working in this field, neither the literature nor my own experience provided any reason for me to suspect prior to the discovery of the presently claimed invention that the amidation of a peptide that was not naturally amidated would produce a beneficial effect upon the bioavailability of any such amidated peptide.

8. I unexpectedly obtained evidence of the effect described in ¶7 above during a series of experiments carried out by me, or under my direction and control, at Unigene for purposes of investigating the effect of oral delivery in dogs on two parathyroid hormone (PTH) analogs. The first such analog was the 1-34 fragment of parathyroid hormone in the free acid form (PTH1-34-OH). The second analog was the amidated 1-31 fragment of parathyroid hormone (PTH1-31-NH_2). I was working with these two analogs to investigate whether there was any difference in the ability of the analogs to induce hypercalcemia in the dogs. There was no expectation that either analog would demonstrate any difference in its bioavailability.

9. Unexpectedly, however, the above-described experiments determined that the oral bioavailability of the amidated PTH fragment (i.e., PTH1-31-NH_2) was dramatically greater than that for the free acid analog (PTH1-34-OH), even though the oral formulation was the same in the case of both peptides. As demonstrated by the data contained in Example 2, Tables 6 and 7 at pp. 52-55 of

the present specification, the mean C_{max} of PTH1-31-NH_2 was 6.25 times greater, and the mean AUC 9.8 times greater, than that of PTH1-34-OH.

10. This observation was confirmed by further experiments carried out by me or under my direction and control involving the oral delivery of amidated vs. non-amidated calcitonin (see Example 1, pp. 50-52) in a dog model, amidated vs. non-amidated PTH 1-34 (see Example 3, pp. 55-57) in a rat model and amidated vs. non-amidated luteinizing hormone releasing hormone (LHRH) (see Example 4, pp. 57-59) in a rat model. In each instance and for all of the peptides tested, the oral bioavailability as measured by the mean C_{max} of the PK profile was dramatically higher for the amidated form of the peptide than for the non-amidated form.

11. This finding of increased bioavailability by the process of amidation of a peptide at a position where the peptide is not naturally amidated has not, to my knowledge and belief, been previously disclosed and could not have been anticipated or obvious to one working in this field based on what was known in the art and/or published in the literature at the time the present application was filed. Furthermore, this unexpected finding is of tremendous commercial importance and, thus, fulfills a long-felt need in this art since increasing the bioavailability of peptides permits a decrease in the cost-of-goods of orally delivered peptide-based pharmaceuticals and thus will allow for the development of more affordable medicaments.

12. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

5/23/08
Date

William Stern